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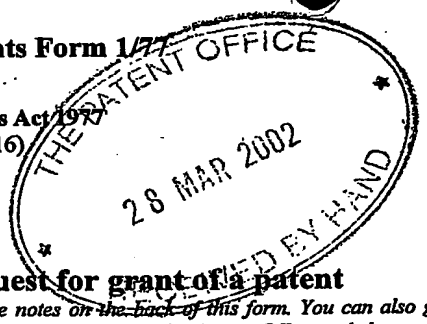

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1/77

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Request for grant of a patent

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28 MAR 2002

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1.	Your reference	**4-32431P1/NFI 8008**
2.	Patent application number *(The Patent Office will fill in this part)*	**0207500.0**
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)* Patent ADP number *(if you know it)* If the applicant is a corporate body, give the country/state of its incorporation	**NOVARTIS AG** **LICHTSTRASSE 35** **4056 BASEL** **SWITZERLAND** 7125487005 **SWITZERLAND**
4.	Title of invention	**Organic compounds**
5.	Name of your agent *(If you have one)* "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)* Patents ADP number *(if you know it)*	**B.A. YORKE & CO.** **CHARTERED PATENT AGENTS** **COOMB HOUSE, 7 ST. JOHN'S ROAD** **ISLEWORTH** **MIDDLESEX TW7 6NH** **1800001** ✓

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7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application		Date of filing (day/month/year)
8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *(see note (d))*	**Yes**		

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11. I/We request the grant of a patent on the basis of this application

Signature: B.A. Yorke & Co.

Date: **28 March 2002**

B.A. Yorke & Co.

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs. E. Cheetham

020 8560 5847

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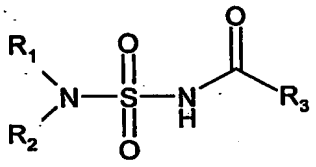
Organic Compounds

The present invention relates to organic compounds, e.g. useful in the treatment of disorders caused by the action of steroid sulfatase.

In one aspect the present invention provides a sulfamic acid amide, such as a compound of formula



I

wherein

R_1 and R_2 together with the nitrogen atom to which they are attached are heterocyclyl, and

R_3 is aryl.

Preferably in a compound of formula I

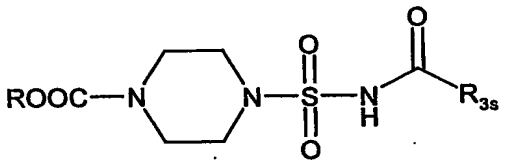
- R_1 and R_2 together with the nitrogen atom to which they are attached are heterocyclyl having 5 to 6 ring members and having beside the nitrogen heteroatom zero, one or more, preferably one, further heteroatoms, e.g. selected from N, O or S; preferably N. such as piperazinyl: e.g. including unsubstituted or substituted heterocyclyl, e.g. heterocyclyl substituted by one or more groups as conventional in organic chemistry, such as alkoxycarbonyl, e.g (C_{1-4})alkoxycarbonyl, e.g. unsubstituted or substituted alkoxycarbonyl, e.g. substituted by a group as conventional in organic chemistry, such as aryl, for example heterocyclyl substituted by tert.butoxycarbonyl, phenylmethyloxycarbonyl; more preferably R_1 and R_2 together with the nitrogen atom to which they are attached are heterocyclyl having 5 to 6 ring members and two nitrogen atoms as heteroatoms, wherein one nitrogen atom is part of the amide function of the sulfamic acid and the second nitrogen atom is substituted by alkoxycarbonyl;
- R_3 is phenyl, e.g. unsubstituted phenyl or substituted phenyl, e.g. substituted by one or more groups as conventional in organic chemistry, e.g. substituted by one or more
  - alkyl, e.g. including (C_{1-4})alkyl, e.g. unsubstituted alkyl or substituted alkyl, e.g. substituted by halogen, such as fluoro, e.g. including trifluoromethyl; or
  - halogen.

A sulfamic acid amide according to the present invention includes an arylcarbonyl sulfamic acid cyclic amide, such as an arylcarbonyl-sulfamic acid N-alkoxycarbonylpiperazinyl-amide.

In another aspect the present invention provides an arylcarbonyl-sulfamic acid N-alkoxycarbonyl-cyclic-amide, such as an arylcarbonyl-sulfamic acid N-alkoxycarbonyl-piperazinyl-amide.

A substitutent of the heterocyclic group in a compound of the present invention, e.g. a substituent of heterocyclyl in a compound of formula I, may be in any position in respect with the arylcarbonylsulfonamide group also attached to said heterocyclyl, e.g. in position 2, 3 or 4; preferably in position 4.

In another aspect the present invention provides a compound of formula



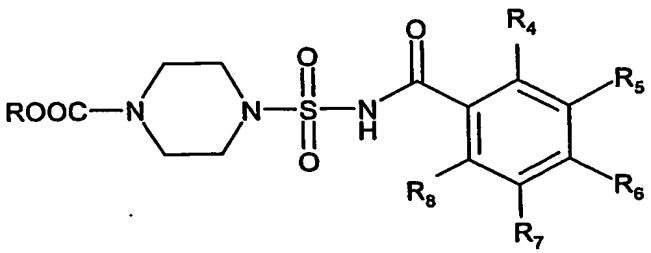
I_s

wherein R is alkyl and R_{3s} is aryl.

In a compound of formula I_s preferably

- R is (C_{1-6})alkyl, including unsubstituted and substituted alkyl, e.g. substituted by aryl, such as tert.butyl or phenyl(C_{1-4})alkyl, e.g. phenylmethyl;
- R_{3s} is phenyl, e.g. unsubstituted phenyl or substituted phenyl, e.g. substituted by one or more group as conventional in organic chemistry, e.g. substituted by one or more
  - alkyl, e.g. including unsubstituted and substituted alkyl, e.g. alkyl substituted by halogen, such as trifluoromethyl;
  - halogen.

In another aspect the present invention provides a compound of formula



I_E

wherein

R is tert.butyl, R_4, R_6 and R_8 are hydrogen and R_5 and R_7 are CF_3;

R is tert.butyl, R_6, R_7 and R_8 are hydrogen and R_4 and R_5 are chloro;

R is tert.butyl, R_4, R_6 and R_8 are hydrogen and R_5 and R_7 are chloro;

R is phenylmethyl, R_4, R_6 and R_8 are hydrogen and R_5 and R_7 are CF_3;

R is phenylmethyl, R_6, R_7 and R_8 are hydrogen and R_4 and R_5 are chloro; or

R is phenylmethyl, R_4, R_6 and R_8 are hydrogen and R_5 and R_7 are chloro.

If not otherwise defined herein aryl includes phenyl; alkyl includes (C_{1-4})alkyl; heterocyclyl includes saturated or unsatured heterocylcyl having 5 to 6 ring members and 1 to 4 heteroatoms, e.g. selected from N,O and S; halogen includes fluoro, chloro, bromo, iodo. Any group may be unsubstituted or substituted, e.g. substituted by a group as conventional in organic chemistry.

Compounds provided by the present invention are hereinafter designated as "compound(s) of (according to) the present invention". A compound of the present invention includes a compound in any form, e.g. in free form, in the form of a salt, in the form of a solvate and in the form of a salt and a solvate.

In another aspect the present invention provides a compound of the present invention in the form of a salt, or in the form of a salt and in the form of a solvate, or in the form of a solvate.

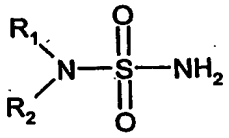
A salt of a compound of the present invention includes a pharmaceutically acceptable salt, e.g. including a metal salt, an acid addition salt or an amine salt. Metal salts include for example alkali or earth alkali salts; acid addition salts include salts of a compound of formula I with an acid, e.g. hydrochloric acid; amine salts include salts of a compound of formula I with an amine.

A compound of the present invention in free form may be converted into a corresponding compound in the form of a salt; and vice versa. A compound of the present invention in free form or in the form of a salt and in the form of a solvate may be converted into a corresponding compound in free form or in the form of a salt in unsolvated form; and vice versa.

A compound of the present invention may e.g. contain asymmetric carbon atoms and may thus exist in the form of enantiomers or diastereoisomeres and mixtures thereof, e.g. racemates. A compound of the present invention may exist in the form of isomers and

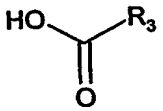
mixtures thereof. Isomeric, e.g. including enantiomeric or diasteromeric, mixtures may be separated as appropriate, e.g. according to a method as conventional, to obtain pure isomers. The present invention includes a compound of the present invention in any isomeric form and in any isomeric mixture.

In another aspect the present invention provides a process for the production of a compound of the present invention comprising reacting a sulfamic acid cyclic amide, wherein one amine group is unsubstituted, e.g. of formula



III

wherein R_1 and R_2 are as defined above,
with an arylcarboxylic acid, e.g. a compound of formula



IV

wherein R_3 is as defined above, e.g. in an activated form, such as in the form of an carboxylic acid chloride, e.g. or in the presence of a coupling agent; and isolating a compound of to the present invention from the reaction mixture obtained.

The above reaction is an acylation reaction and may be carried out as appropriate, e.g. in appropriate solvent and at appropriate temperatures, e.g. according to a method as conventional or according to a method as described herein.

A sulfamic acid cyclic amide wherein one amine group is unsubstituted, such as a compound of formula III, may e.g. be obtained from a corresponding sulfonic acid (cyclic amide), by reaction with amidosulfonylchloride, e.g. in the presence of an amide. Compounds of formula II, III and IV are known or may be obtained as appropriate, e.g. according to a method as conventional or as described herein. Any compound described herein, e.g. a compound of the present invention, may be prepared as appropriate, e.g. according to a method as conventional, e.g. or as described herein.

In the following examples which illustrate the invention references to temperature are in degrees Celsius. ^{1}HNMR are carried out in $CDCl_3$ if not otherwise indicated.
Abbreviations used: m.p.: melting point. RT: room temperature; BOC: tert.butyloxycarbonyl.

Example 1

3,5-Bis(trifluoromethyl)benzoyl-sulfamic acid N-BOC-piperazineamide

A) N-BOC-piperazine-N'-sulfamate

To a solution of 1 g of BOC-piperazine and 1.085 g of triethylamine are added 612 mg of amidosulfonyl chloride in 20 ml of CH_2Cl_2. The mixture obtained is stirred for ca. 6 hours at 0° and allowed to warm to RT overnight. The solvent of the mixture obtained is evaporated off, the evaporation residue obtained is dissolved in ethyl acetate, washed with H_2O, dried and concentrated. The concentration residue obtained is subjected to chromatography on silicagel. N-BOC-piperazine-N'-sulfamate in crystalline form is obtained. m.p.: 167-171°.

B) 3,5-Bis(trifluoromethyl)benzoyl-sulfamic acid N-BOC-piperazineamide

To a solution of 195 mg of N-BOC-piperazine-N'-sulfamate and 148 mg of triethylamine are added 406 mg of 3,5-bis(trifluoromethyl)benzoylchloride in 50 ml of CH_2Cl_2. The mixture obtained is stirred for ca. 20 hours at RT, the solvent is evaporated off, the evaporation residue obtained is dissolved in ethyl acetate, washed with H_2O, dried and concentrated. The concentration residue obtained is subjectd to chromatograpy on silica gel. 265 mg of 3,5-bis(trifluoromethyl)benzoyl-sulfamic acid N-BOC-piperazineamide in crystalline form are obtained. m.p.: 185-190°. ^{1}H-NMR δ: 1.4 (s, 9 H, BOC), 3.0-3.2 (m, 4 H), 3.3-3.5 (m, 4 H), 7.78 (s, 1 H), 8.28 (s, 2 H).

According to the method as described in example 1 but using the appropriate starting materials the following compounds of examples 2 to 6 are obtained:

Example 2

2,3-Dichlorobenzoyl-sulfamic acid N-BOC-piperazineamide

m.p.: 172-175°. ^{1}H-NMR δ: 1.48 (s, 9 H, BOC), 3.45 (m, 4 H), 3.55 (m, 4 H), 7.35 (t, ^3J = 2 Hz, 1 H), 7.55 (dd, ^4J = 2 Hz and ^3J = 4 Hz, 1 H), 7.65 (dd, ^4J = 2 Hz and ^3J = 4 Hz, 1 H).

Example 3

3,5-Dichlorobenzoyl-sulfamic acid N-BOC-piperazineamide

m.p.: 200-203°. ^{1}H-NMR δ: 1.45 (s, 9 H, BOC), 3.45 (m, 4 H), 3.55 (m, 4 H), 7.60 (t, ^4J = 2 Hz, 1 H), 8.28 (d, ^4J = 2 Hz, 2 H).

Example 4

3,5-Bis(trifluoromethyl)benzoyl-sulfamic acid N-phenylmethyloxycarbonyl-piperazineamide

m.p.: 208-211°. ^{1}H-NMR δ: 3.5 (m, 4 H), 3.65 (m, 4 H), 5.12 (s, 2 H, OCH_2), 7.30-7.40 (m, 5 H, H-Ar), 8.10 (s, 1 H), 8.30 (s, 2 H), 8.90 (broad s, 1 H, NH).

Example 5

2,3-Dichlorobenzoyl-sulfamic acid N-phenylmethyloxycarbonyl-piperazineamide

m.p.: 63-67°. ^{1}H-NMR δ: 3.51 (t, ^{3}J = 5 Hz, 4 H), 3.65 (t, ^{3}J = 5 Hz, 4 H), 5.15 (s, 2 H, OCH_2), 7.30-7.40 (m, 6 H, H-Ar), 7.55 (dd, ^{3}J = 8 Hz and ^{4}J = 1.6 Hz, 1 H), 7.65 (dd, ^{3}J = 8 Hz and ^{4}J = 1.6 Hz, 1 H), 8.38 (broad s, 1 H, NH).

Example 6

3,5-Dichlorobenzoyl-sulfamic acid N-phenylmethyloxycarbonyl-piperazineamide

m.p.: 205-208°. ^{1}H-NMR δ: 3.47 (t, ^{3}J = 5 Hz, 4 H), 3.62 (t, ^{3}J = 5 Hz, 4 H), 5.14 (s, 2 H, OCH_2), 7.32-7.38 (m, 5 H, H-Ar), 7.60 (t, ^{4}J = 2 Hz, 1 H), 7.65 (s, ^{4}J = 2 Hz, 2 H), 8.37 (broad s, 1 H, NH).

Steroidal hormones in particular tissues are associated with several diseases, such as tumors of breast, endometrium and prostate and disorders of the pilosebaceous unit, e.g. acne, androgenetic alopecia, and hirsutism. Important precursors for the local production of these steroid hormones are steroid 3-O-sulfates which are desulfated by the enzyme steroid sulfatase in the target tissues. Inhibition of this enzyme results in reduced local levels of the corresponding active steroidal hormones, which is expected to be of therapeutic relevance. Furthermore, steroid sulfatase inhibitors may be useful as immunosuppressive agents, and have been shown to enhance memory when delivered to the brain.

Acne is a polyetiological disease caused by the interplay of numerous factors, such as inheritance, sebum, hormones, and bacteria. The most important causative factor in acne is sebum production; in almost all acne patients sebaceous glands are larger and more sebum is produced than in persons with healthy skin. The development of the sebaceous gland and the extent of sebum production is controlled hormonally by androgens; therefore, androgens play a crucial role in the pathogenesis of acne. In man, there are two major sources supplying androgens to target tissues: (i) the gonades which secrete testosterone, (ii) the adrenals producing dehydroepiandrosterone (DHEA) which is secreted as the sulfate conjugate (DHEAS). Testosterone and DHEAS are both converted to the most active

androgen, dihydrotestosterone (DHT), in the target tissue, e.g. in the skin. There is evidence that these pathways of local synthesis of DHT in the skin are more important than direct supply with active androgens from the circulation. Therefore, reduction of endogeneous levels of androgens in the target tissue by specific inhibitors is expected be of therapeutic benefit in acne and seborrhoea. Furthermore, it opens the perspective to treat these disorders through modulation of local androgen levels by topical treatment, rather than influencing circulating hormone levels by systemic therapies.

Androgenetic male alopecia is very common in the white races, accounting for about 95% of all types of alopecia. Male-pattern baldness is caused by an increased number of hair follicles in the scalp entering the telogen phase and by the telogen phase lasting longer. It is a genetically determined hair loss effected through androgens. Elevated serum DHEA but normal testosterone levels have been reported in balding men compared with non-balding controls, implying that target tissue androgen production is important in androgenetic alopecia.

Hirsutism is the pathological thickening and strengthening of the hair which is characterized by a masculine pattern of hair growth in children and women. Hirsutism is androgen induced, either by increased formation of androgens or by increased sensitivity of the hair follicle to androgens.

Therefore, a therapy resulting in reduction of endogeneous levels of androgens and/or estrogens in the target tissue (skin) should be effective in acne, androgenetic alopecia and hirsutism.

As described above, DHT, the most active androgen, is synthesized in the skin from the abundant systemic precursor DHEAS and the first step in the metabolic pathway from DHEAS to DHT is desulfatation of DHEAS by the enzyme steroid sulfatase to produce DHEA. The presence of the enzyme in keratinocytes and in skin-derived fibroblasts has been described. The potential use of steroid sulfatase inhibitors for the reduction of endogenous levels of steroid hormones in the skin was confirmed using known steroid sulfatase inhibitors, such as estrone 3-O-sulfamate and 4-methylumbelliferyl-7-O-sulfamate. We have found that inhibitors of placental steroid sulfatase also inhibit steroid sulfatase prepared from either a human keratinocyte (HaCaT) or a human skin-derived fibroblast cell line (1BR3GN). Such inhibitors were also shown to block steroid sulfatase in intact monolayers of the HaCaT keratinocytes.

Therefore, inhibitors of steroid sulfatase can be used to reduce androgen and estrogen levels in the skin. They can be used as inhibitors of the enzyme steroid sulfatase for the local

treatment of androgen-dependent disorders of the pilosebaceous unit (such as acne, seborrhoea, androgenetic alopecia, hirsutism) and for the local treatment of squamous cell carcinoma.

Furthermore non-steroidal steroid sulfatase inhibitors are expected to be useful for the treatment of disorders caused by the action of steroid hormones in which the steroidal products of the sulfatase cleavage play a role. Indications for these new kind of inhibitors include androgen-dependent disorders of the pilosebaceous unit (such as acne, seborrhea, androgenetic alopecia, hirsutism); estrogen- or androgen-dependent tumors, such as squamous cell carcinoma and neoplasms, e.g. of the breast, endometrium, and prostate; inflammatory and autoimmune diseases, such as rheumatoid arthritis, type I and II diabetes, systemic lupus erythematosus, multiple sclerosis, myastenia gravis, thyroiditis, vasculitis, ulcerative colitis, and Crohn's disease, psoriasis, contact dermatitis, graft versus host disease, eczema, asthma and organ rejection following transplantation.

Steroid sulfatase inhibitors are also useful for the treatment of cancer, especially for the treatment of estrogen- and androgen-dependent cancers, such as cancer of the breast and endometrium and squamous cell carcinoma, and cancer of the prostata.

Steroid sulfatase inhibitors are also useful for the enhancement of cognitive function, especially in the treatment of senile dementia, including Alzheimer's disease, by increasing the DHEAS levels in the central nervous system.

Activities of the compounds of the present invention as inhibitors of steroid sulfatase may be shown in the following test systems (assays):

Purification of human steroid sulfatase

Human placenta is obtained freshly after delivery and stripped of membranes and connective tissues. For storage, the material is frozen at -70°C. After thawing, all further steps are carried out at 4°C, while pH values are adjusted at 20°C. 400 g of the tissue is homogenized in 1.2 l of buffer A (50 mM Tris-HCl, pH 7.4, 0.25 M sucrose). The homogenate is centrifuged at 10,000xg for 45 minutes. The supernatant is set aside and the pellet obtained is re-homogenized in 500 ml buffer A. After centrifugation, the two supernatants are combined and subjected to ultracentrifugation (100,000xg, 1 hour). The pellet obtained is resuspended in buffer A and the centrifugation is repeated. The pellet obtained is suspended in 50 ml of 50 mM Tris-HCl, pH 7.4 and stored at -20°C until further work-up.

After thawing, microsomes are collected by ultracentrifugation (as above) and suspended in 50 ml buffer B (10 mM Tris-HCl, pH 7.0, 1 mM EDTA, 2 mM 2-mercaptoethanol, 1 % Triton X-100, 0.1 % aprotinin). After 1 hour on ice with gentle agitation, the suspension obtained is centrifuged (100,000xg, 1 hour). The supernatant containing the enzyme activity is collected and the pH is adjusted to 8.0 with 1 M Tris. The solution obtained is applied to a hydroxy apatite column (2.6x20 cm) and equilibrated with buffer B, pH 8.0. The column is washed with buffer B at a flow rate of 2 ml/min. The activity is recovered in the flow-through. The pool is adjusted to pH 7.4 and subjected to chromatography on a concanavalin A sepharose column (1.6x10 cm) equilibrated in buffer C (20 mM Tris-HCl, pH 7.4, 0.1 % Triton X-100, 0.5 M NaCl). The column is washed with buffer C, and the bound protein is eluted with 10 % methyl mannoside in buffer C. Active fractions are pooled and dialysed against buffer D (20 mM Tris-HCl, pH 8.0, 1 mM EDTA, 0.1 % Triton X-100, 10 % glycerol (v/v)).
The retentate obtained is applied to a blue sepharose column (0.8x10 cm) equilibrated with buffer D; that column is washed and eluted with a linear gradient of buffer D to 2 M NaCl in buffer D. Active fractions are pooled, concentrated as required (Centricon 10), dialysed against buffer D and stored in aliquots at -20°C.

Assay of human steroid sulfatase

It is known that purified human steroid sulfatase not only is capable to cleave steroid sulfates, but also readily cleaves aryl sulfates such as 4-methylumbelliferyl sulfate which is used herein. Assay mixtures are prepared by consecutively dispensing the following solutions into the wells of white microtiter plates:

1) 50 µl substrate solution (1.5 mM 4-methylumbelliferyl sulfate in 0.1 M Tris-HCl, pH 7.5)
2) 50 µl test compound dilution in 0.1 M Tris-HCl, pH 7.5, 0.1 % Triton X-100 (stock solutions of the test compounds are prepared in DMSO; final concentrations of the solvent in the assay mixture does not exceed 1 %)
3) 50 µl enzyme dilution (approximately 12 enzyme units/ml)
   We define one enzyme unit as the amount of steroid sulfatase that hydrolyses 1 nmol of 4-methylumbelliferyl sulfate per hour at an initial substrate concentration of 500 µM in 0.1 M Tris-HCl, pH 7.5, 0.1 % Triton X-100, at 37°C.

Plates are incubated at 37°C for 1 hour. The reaction is stopped by addition of 100 µl 0.2 M NaOH. Fluorescence intensity is determined in a Titertek Fluoroskan II instrument with λ_{ex} = 355 nm and λ_{em} = 460 nm.

Calculation of relative IC_{50} values

From the fluorescence intensity data (I) obtained at different concentrations (c) of the test compound in the assay described above, the concentration inhibiting the enzymatic activity by 50 % (IC_{50}) is calculated using the equation

$$I = \frac{I_{100}}{1 + (c / IC_{50})^s}$$

wherein I_{100} is the intensity observed in the absence of inhibitor and s is a slope factor. Estrone sulfamate serves as a reference compound and its IC_{50} value is determined in parallel to all other test compounds. Relative IC_{50} values are defined as follows:

$$\text{rel } IC_{50} = \frac{IC_{50} \text{ of test compound}}{IC_{50} \text{ of estrone sulfamate}}$$

Estrone sulfamate showed an IC_{50} value of approximately 60 nM. The compounds of the present invention inhibit steroid sulfatase in the above described assay.

CHO/STS assay

CHO cells stably transfected with human steroid sulfatase (CHO/STS) are seeded into microtiter plates. After reaching approximately 90% confluency, they are incubated overnight with graded concentrations of test substances. They are then fixed with 4% paraformaldehyde for 10 minutes at room temperature and washed 4 times with PBS, before incubation with 100µl/well 0.5mM 4-methylumbelliferyl sulfate (MUS), dissolved in 0.1M Tris-HCl, pH 7.5. The enzyme reaction is carried out at 37° for 30 minutes. Then 50 µl/well stop solution (1M Tris-HCl, pH 10.4) are added. The enzyme reaction solutions are transferred to white plates (Microfluor, Dynex, Chantilly, VA) and read in a Fluoroskan II fluorescence microtiter plate reader. Reagent blanks are subtracted from all values. For drug testing, the fluorescence units (FU) are divided by the optical density readings after staining cellular protein with sulforhodamine B (OD_{550}), in order to correct for variations in cell number. IC_{50} values are determined by linear interpolation between two bracketing points. In each assay with inhibitors, estrone 3-O-sulfamate is run as a reference compound, and the IC_{50} values are normalized to estrone 3-O-sulfamate (relative IC_{50} = IC_{50} compound / IC_{50} estrone 3-O-sulfamate). The compounds of the present invention inhibit steroid sulfatase in the above described assay.

The compounds of the present invention are therefore indicated for use as steroid sulfatase inhibitors, e.g. in the prevention or treatment of disorders caused by the action of steroid sulfatase; e.g. in the treatment of androgen-dependent disorders of the pilosebaceous unit, such as acne, seborrhea, androgenetic alopecia, hirsutism and for the treatment of cancer, especially of estrogen and androgen-dependent cancers, and for treatment of cognitive dysfunction, such as senile dementia including Alzheimer's disease.
The use of a sulfamic acid amide according to the present invention, as a steroid sulfatase inhibitor is novel.

In another aspect the present invention provides

- the use of a sulfamic acid amide, e.g. a sulfamic acid amide according to the present invention, as a steroid sulfatase inhibitor; and
- a method for the prevention or treatment of disorders caused by steroid sulfatase activity comprising administering an effective amount of at least sulfamic acid amide, e.g. a sulfamic acid amide according to the present invention, to a subject in need of such treatment, e.g. including prevention or treatment of androgen-dependent disorders of the pilosebaceous unit, such as acne, seborrhea, androgenetic alopecia, hirsutism; e.g. and including the treatment of cancer, especially of estrogen and androgen-dependent cancers, and the treatment of cognitive dysfunction, such as senile dementia including Alzheimer's disease.

For this use the dosage to be used will vary, of course, depending e.g. on the particular compound employed, the mode of administration and the treatment desired. In general, satisfactory results may be obtained if the compounds are administered at a daily dose of from about 0.1 mg/kg to about 100 mg/kg animal body weight, e.g. conveniently administered in divided doses two to four times daily. For most large mammals the total daily dosage may be from about 5 mg to about 5000 mg, e.g. conveniently administered in divided doses up to four times a day or in retarded form. Unit dosage forms may comprise, e.g. from about 1.25 mg to about 2000 mg of the compounds in admixture with at least one, e.g. solid or liquid, pharmaceutically acceptable carrier/diluent.

The compounds of the present invention may be administered in the form of a pharmaceutically acceptable salt, e.g. an acid addition salt, metal salt, amine salt; or in free form; optionally in the form of a solvate. The compounds of the present invention in the

form of a salt, or in the form of a salt and a solvate, or in the form of a solvate exhibit the same order of activity as the compounds of the present invention in free unsolvated form. The compounds of the present invention may be administered in similar manner to known standards for use in such indications. The compounds of the present invention may be admixed with pharmaceutically acceptable carriers/diluents and optionally further excipients, e.g. including carriers/diluents and excipients such as conventional; and may be administered, e.g. orally, e.g. in the form of pharmaceutical compositions, e.g. in the form of tablets and capsules. Alternatively, the compounds of the present invention may be administered parenterally or intravenously; and e.g. topically, e.g. in the form of pharmaceutical compositions, e.g. ointments or creams. The concentrations of the active substance will of course vary, e.g. depending on the compound employed, the treatment desired and the nature of the pharmaceutical composition used. In general, satisfactory results may be obtained, e.g. in topical formulations, at concentrations of from about 0.05 to about 5.0 %, such as from about 0.1 to about 1.0 % by weight.

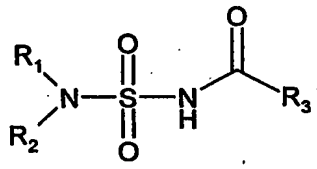
In another aspect the present invention provides

- a pharmaceutical composition comprising at least one compound of the present invention in association with a pharmaceutically acceptable carrier/diluent;
- a process for the preparation of a pharmaceutical composition comprising admixing at least one compound of the present invention with a pharmaceutically acceptable carrier/diluent;
- a compound of the present invention for use as a pharmaceutical, e.g. in the prevention or treatment of disorders caused by the action of steroid sulfatase; such as in the prevention or treatment of disorders of androgen-dependent disorders of the pilosebaceous unit, e.g. acne, seborrhoea, androgenetic alopecia, hirsutism, e.g. and for treatment of cancer, such as of estrogen and androgen-dependent cancers; e.g. and for treatment of cognitive dysfunction, such as senile dementia including Alzheimer's disease; and
- a compound of the present invention for use in the preparation of a medicament in the prevention or treatment of disorders caused by the action of steroid sulfatase.

Patent claims

1. An arylcarbonyl sulfamic acid cyclic amide.

2. A compound of formula

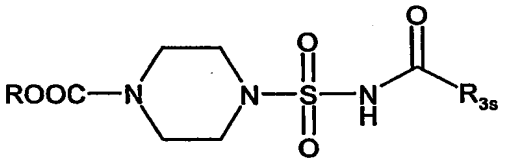


I

wherein

R_1 and R_2 together with the nitrogen atom to which they are attached are heterocyclyl, and R_3 is aryl.

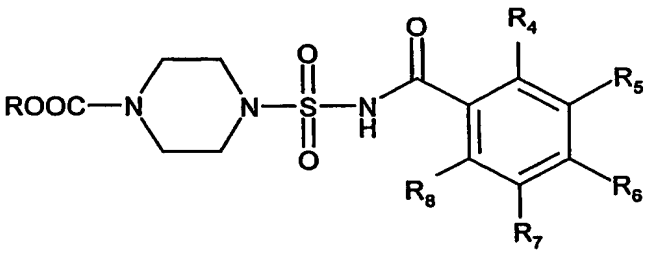
3. A compound of formula



I_s

wherein R is alkyl and R_{3s} is aryl.

4. A compound of formula



I_E

wherein

R is tert.butyl, R_4, R_6 and R_8 are hydrogen and R_5 and R_7 are CF_3;

R is tert.butyl, R_6, R_7 and R_8 are hydrogen and R_4 and R_5 are chloro;

R is tert.butyl, R_4, R_6 and R_8 are hydrogen and R_5 and R_7 are chloro;

R is phenylmethyl, R_4, R_6 and R_8 are hydrogen and R_5 and R_7 are CF_3;

R is phenylmethyl, R_6, R_7 and R_8 are hydrogen and R_4 and R_5 are chloro; or

R is phenylmethyl, R_4, R_6 and R_8 are hydrogen and R_5 and R_7 are chloro.

5. A compound of any one of claims 1 to 4 in the form of a salt, or in the form of a salt and in the form of a solvate, or in the form of a solvate.

6. Use of a sulfamic acid amide as a steroid sulfatase inhibitor.

7. A method for the prevention or treatment of disorders caused by steroid sulfatase activity comprising administering an effective amount of at least one compound according to any one of claims 1 to 5 to a subject in need of such treatment.

8. A pharmaceutical composition comprising at least one compound of any one of claims 1 to 5 in association with a pharmaceutically acceptable carrier/diluent.

9. A compound of any one of claims 1 to 5 for use as a pharmaceutical.

10. A compound of any one of claims 1 to 5 for use in the preparation of a medicament in the prevention or treatment of disorders caused by the action of steroid sulfatase.

Abstract

Sulfamic acid (cyclic) amides and their use as a pharmaceutical in the prevention or treatment of disorders caused by steroid sulfatase activity.

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